



ResMed

*Changing lives
with every breath*

➤ ResMed's Clinical Strategy — 20 million lives by 2020

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ResMed's Clinical Strategy — Sleep Apnea and Beyond

- Clinical Perspective on SDB
- Core market
 - Obstructive Sleep Apnea
- Adjacent Markets
 - Respiratory Failure
 - Central Sleep Apnea
- Serve HF
 - What do the results mean
- Where to from here?

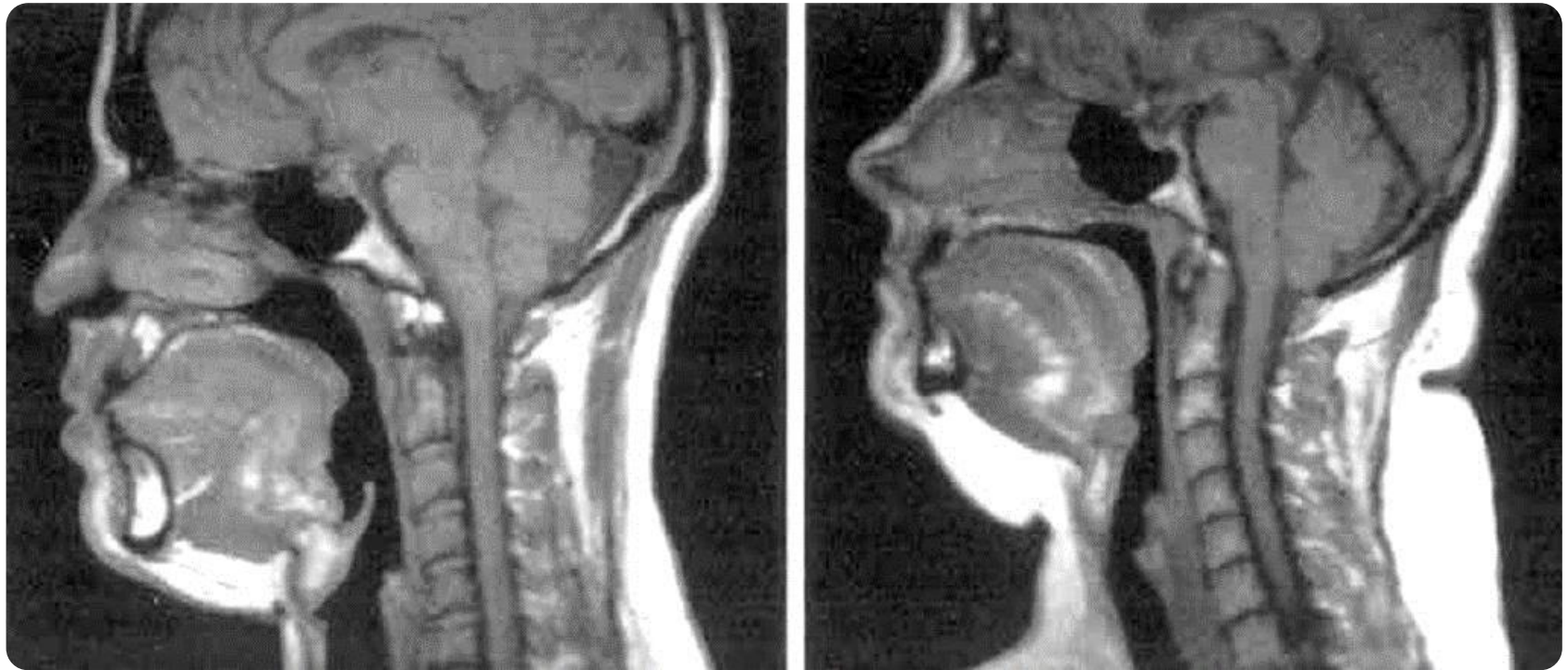


➤ Sleep Disordered Breathing

- 3 very different abnormal patterns of breathing during sleep
 - Obstructive sleep apnea
 - Central sleep apnea
 - Respiratory failure
- OSA is easily the most common — affecting approximately 26% of the general adult population
- OSA accounts for over 80% of patients
- CSA accounts for 10% of patients



> OSA and Upper Airway Collapse





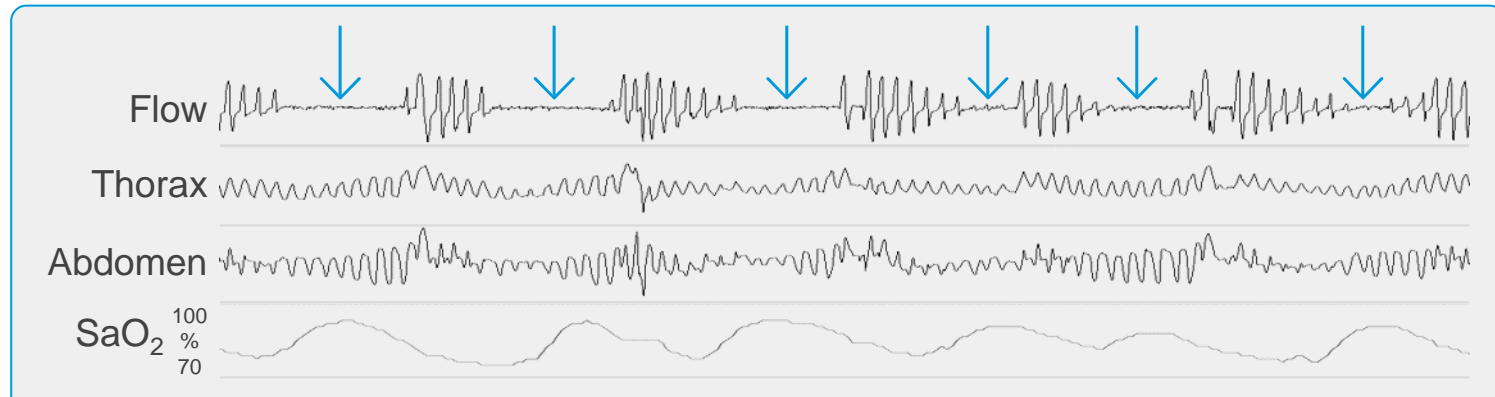
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OSA

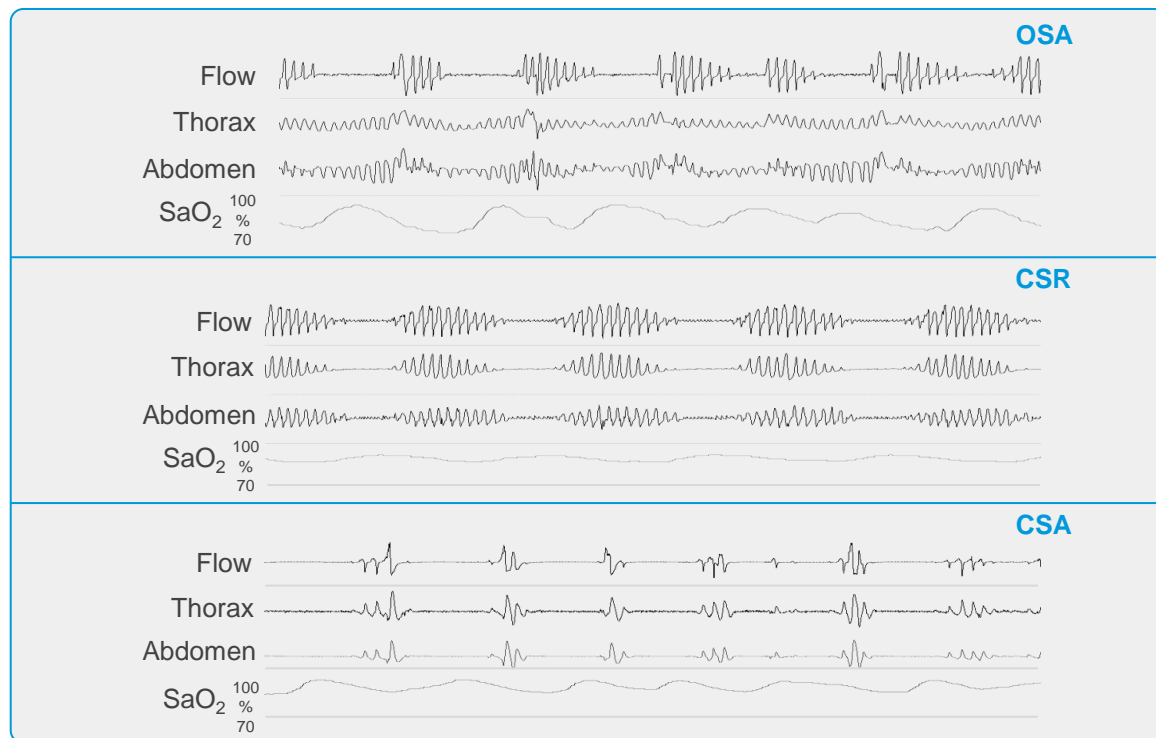
> Apnea Hypopnea Index



- **Apnea Hypopneas Index is a measure of severity**
- **AHI is the number of events divided by time asleep**
 - AHI less than 5 is considered normal
 - AHI from 5 to 15 is mild sleep apnea
 - AHI from 15 to 30 is moderate sleep apnea
 - AHI above 30 is severe sleep apnea



Obstructive vs. Central Sleep Apnea



> Symptoms

- Men present with “typical” OSA symptoms
 - Snoring
 - Witnessed apneas
 - Daytime sleepiness
- Women often present with different symptoms, causing misdiagnosis
 - Insomnia
 - Restless legs
 - Fatigue/depression
 - Headaches and muscle pain



OSA reduces quality of life — CPAP improves quality of life

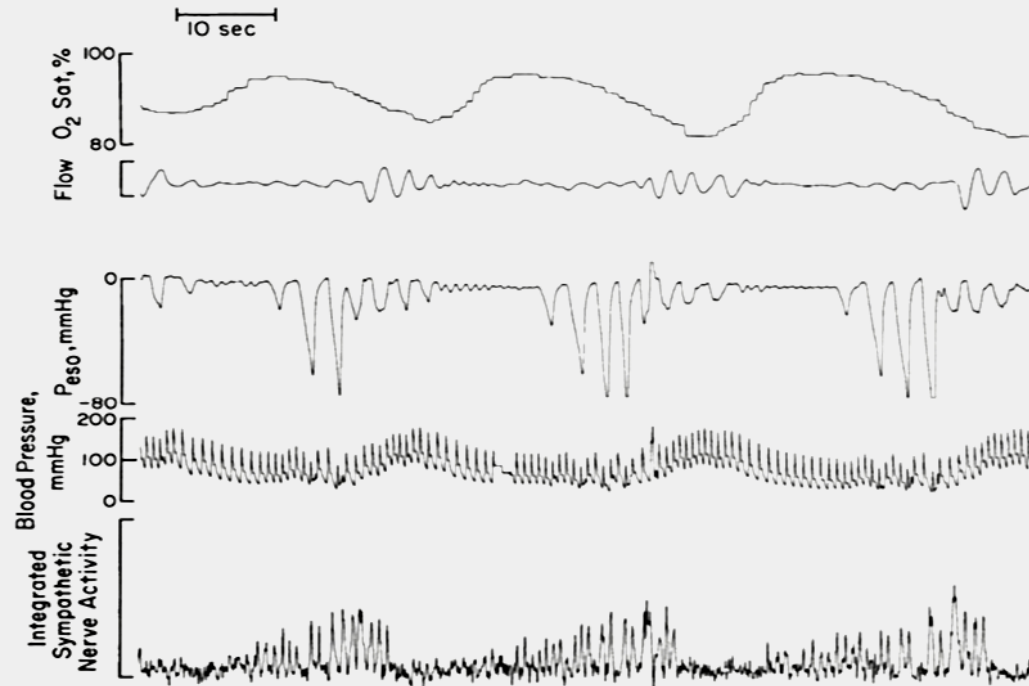


Cardiovascular Consequences of Sleep Apnea

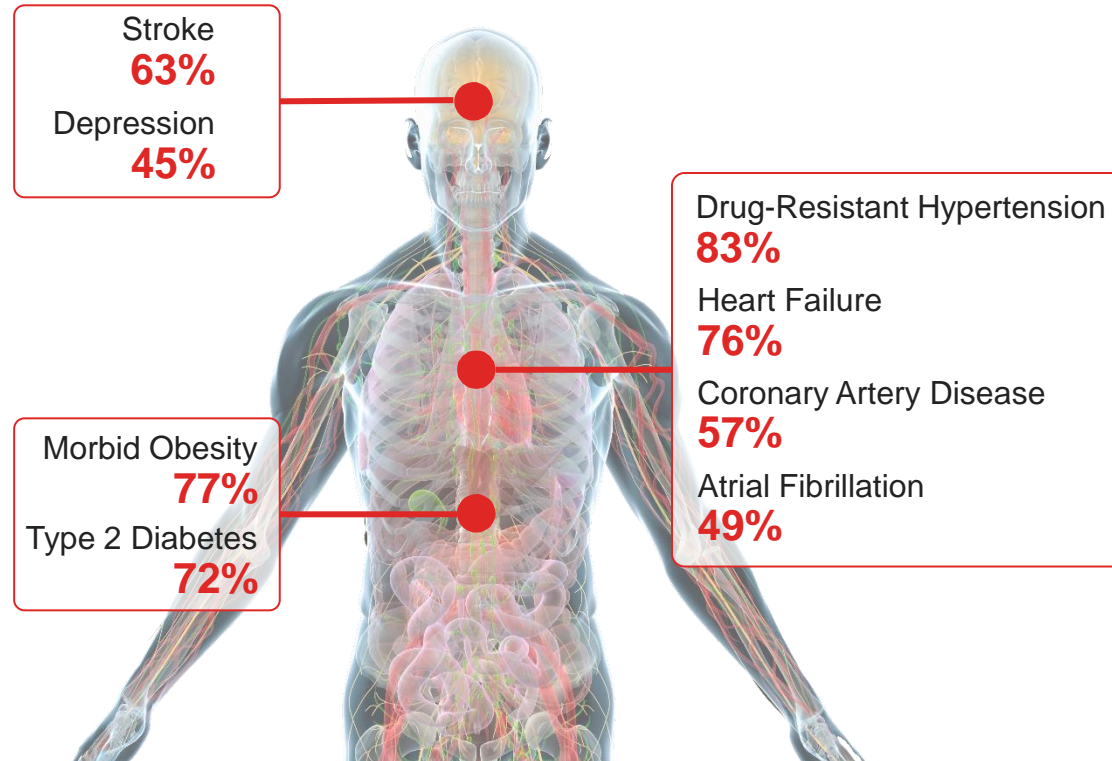
Negative swings
in intra-thoracic
pressure

Increase in
blood pressure

Surge in
sympathetic
nerve activity

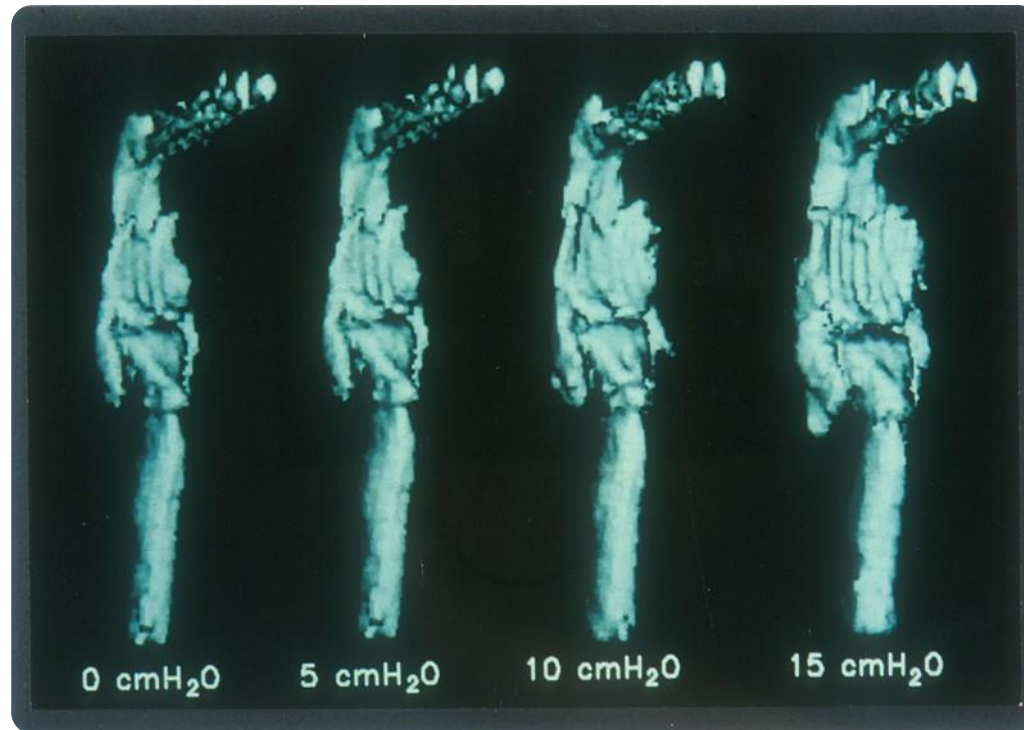


> Sleep Apnea: Highly prevalent in key chronic diseases



References: Logan et al. *J. Hypertension*; O'Keefe and Patterson, *Obes Surgery*; Oldenburg et al., *Eur J Heart Failure*; Einhorn et al. *Endocrine Prac*; Basseti et al. *Stroke*

> Effect of CPAP on Upper Airway





PAP Patient Interfaces: smaller, quieter, more comfortable

Over the past 25 years there have been large improvements in the equipment used for treatment



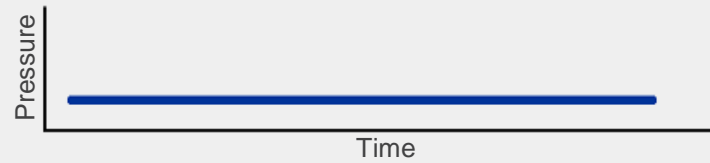
> PAP Flow Generators: smaller, quieter, more comfortable



> Positive Airway Pressure (PAP) Therapy

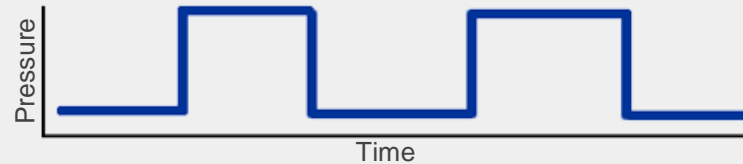
1) CPAP

CPAP

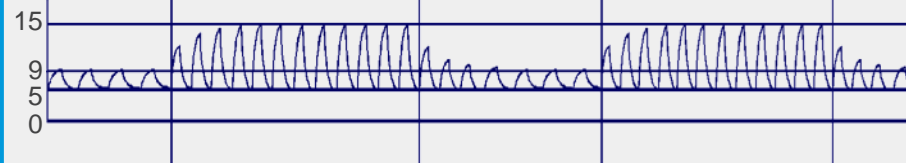


2) Bi-level (VPAP)

VPAP

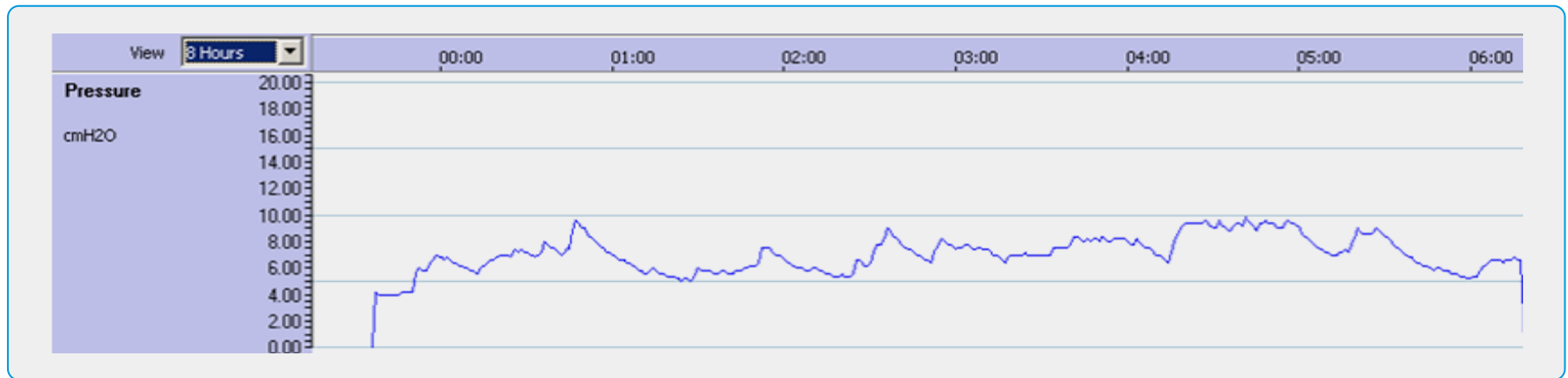


3) ASV

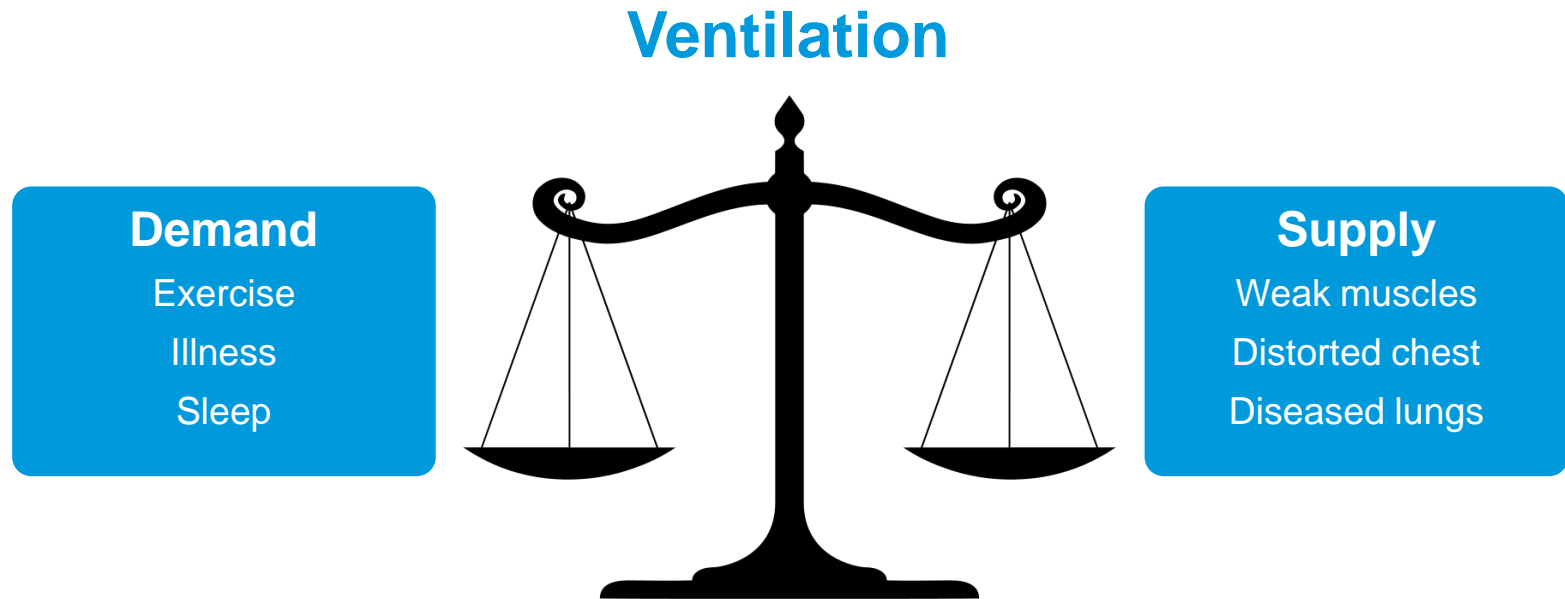


> Automatic Positive Airway Pressure (APAP)

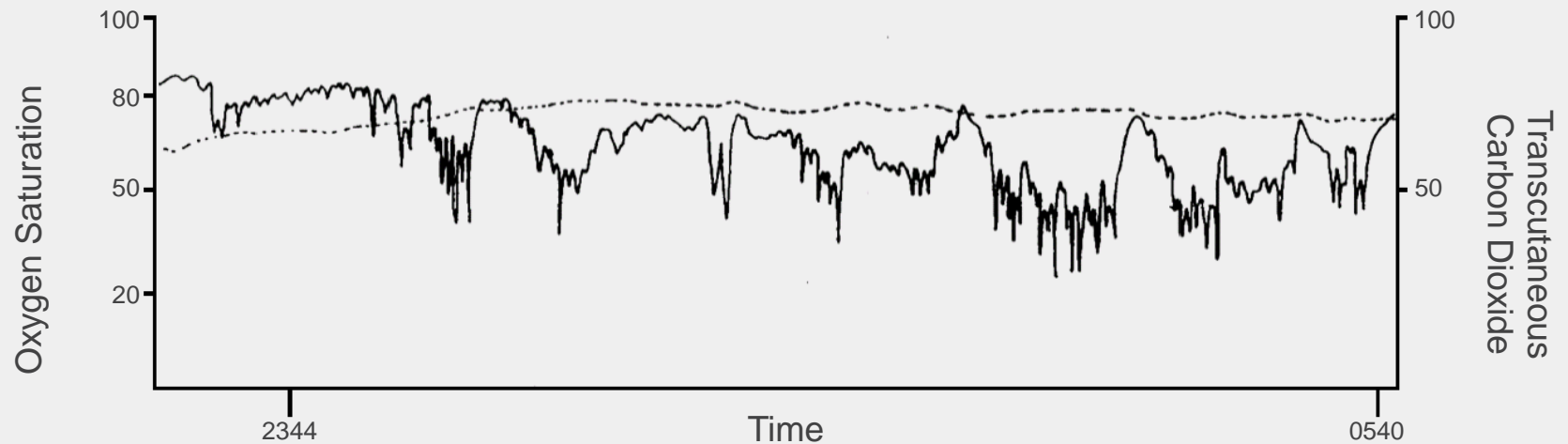
- Used in long term therapy or titration
- Raises pressure to prevent events and lowers it if no events
- Monitor flow to predict events
 - Apnea
 - Hypopnea
 - Snoring
 - Flow limitation



> Respiratory Failure and Ventilation



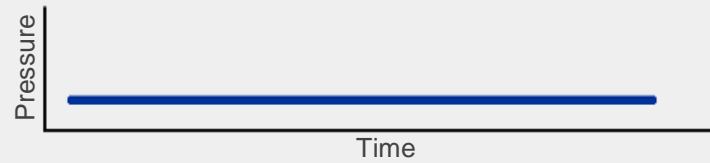
> Respiratory Failure



> Positive Airway Pressure (PAP) Therapy

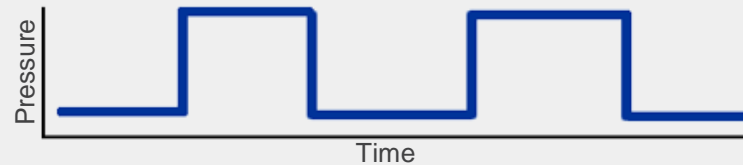
1) CPAP

CPAP

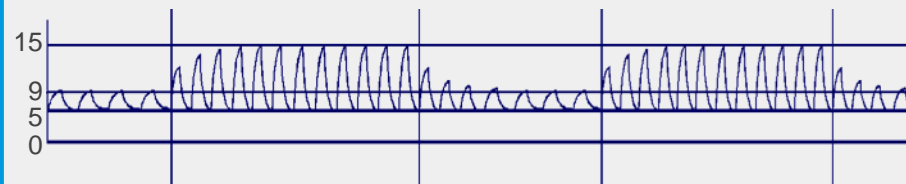


2) Bi-level (VPAP)

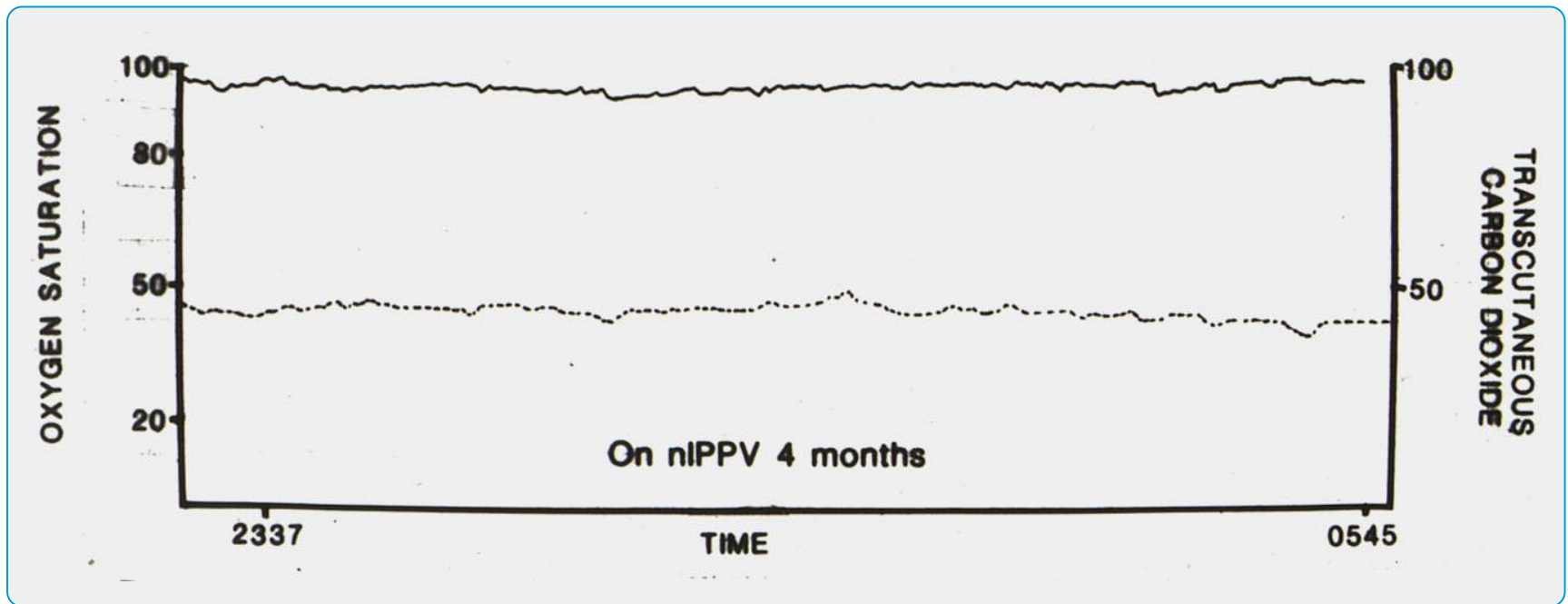
VPAP



3) ASV

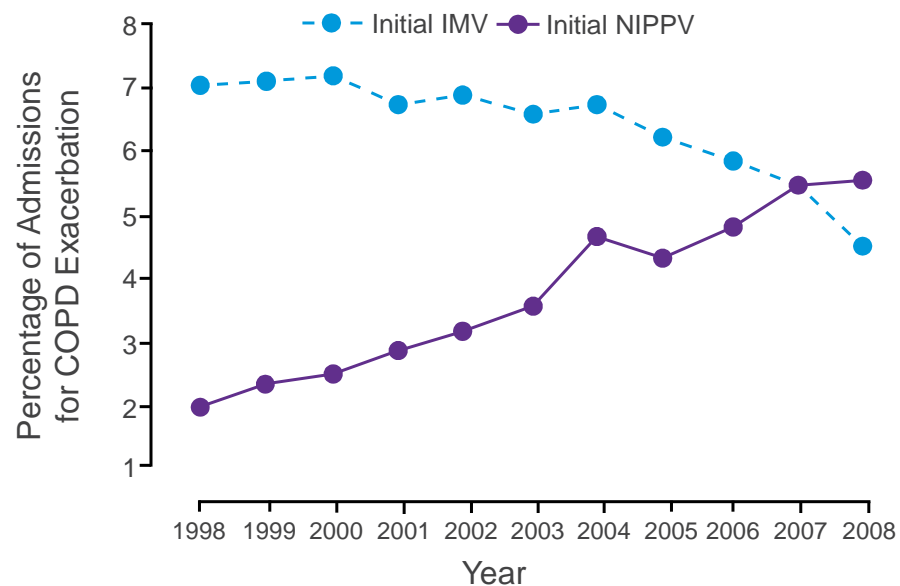


> Respiratory Failure Treated





Ventilation for Acute COPD

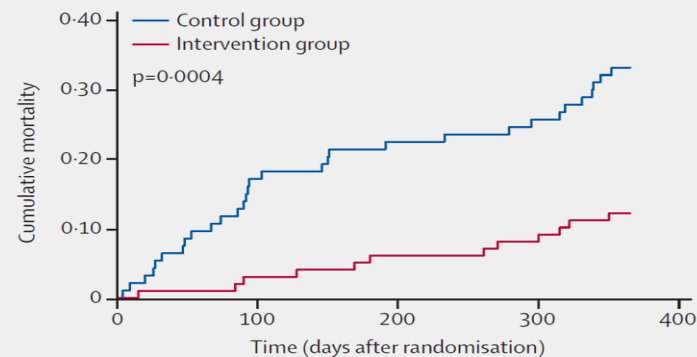


References: Chandra et al, AJRCCM online pub 20 October 2011

THE LANCET Respiratory Medicine

Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial

Thomas Köhnlein, Wolfram Windisch, Dieter Köhler, Anna Drabik, Jens Geiseler, Sylvia Hartl, Ortrud Karg, Gerhard Laier-Groeneveld, Stefano Nava, Bernd Schönhofer, Bernd Schucher, Karl Wegscheider, Carl P Criée, Tobias Welte



Number at risk

Control group	93	77	72	69
Intervention group	102	95	92	90

➤ Our new respiratory care platform

Life Support Ventilation



Astral™

- Designed to enrich life for patients
 - Greater freedom
 - Versatile choices
 - Saves time, so that clinicians and staff can focus on patients



reddot design award
product design 2014

➤ Central Sleep Apnea

- Abnormal breathing due to problems with respiratory control

1. Complex Sleep Apnea/ Mixed Sleep Apnea

- Associated with OSA (5 to 10% of sleep studies)

2. Opioid induced CSA

- Chronic users of prescribed narcotics

3. Associated with chronic diseases

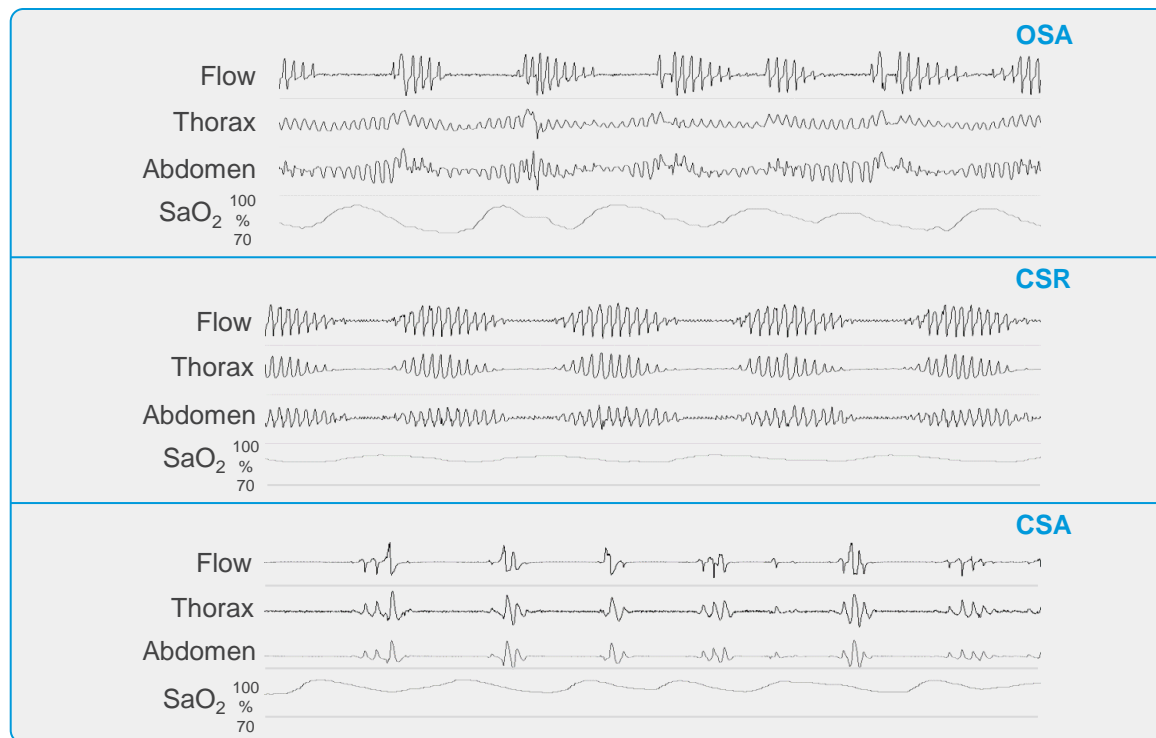
- Heart failure, diabetes, renal failure, stroke

- ASV is used to treat all of these subgroups
 - Complex SA accounts for most prescriptions
 - Around 25% of scripts are for heart failure



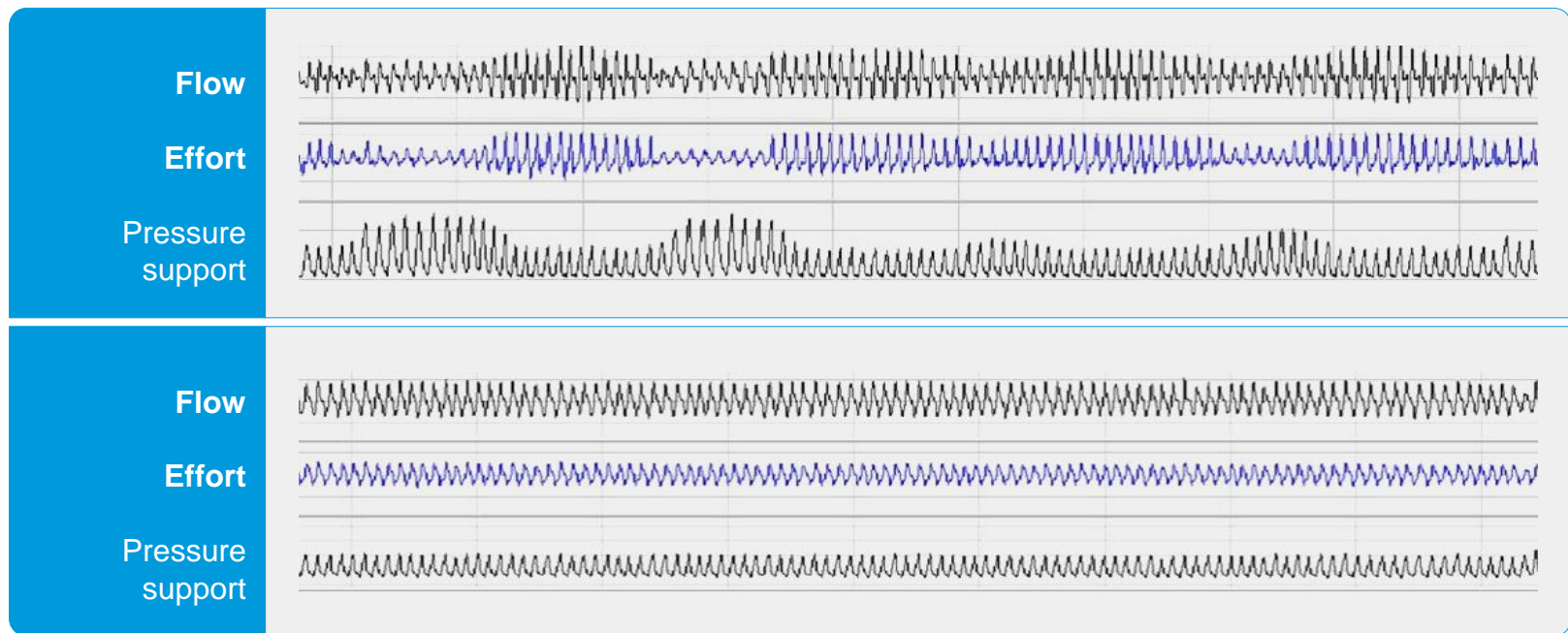


Obstructive vs. Central Sleep Apnea



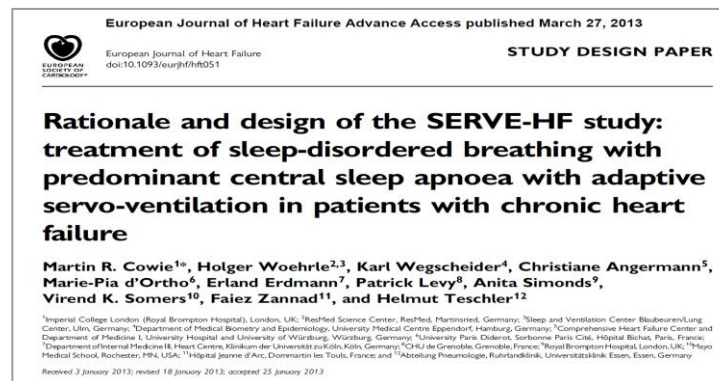
> Adaptive Servo Ventilation

Adaptive Servo Ventilation — mechanism of action



- Primary endpoint
 - Time to first event of all cause mortality or unplanned hospitalization for worsening heart failure
- Secondary endpoints
 - Quality of Life (MLWHF, Euroquol)
 - Exercise Tolerance (6 MWD)
 - NYHA class
- Major substudy
 - Left ventricular function and BNP
 - Sleep

- Multi-center, outcome study
 - Comparing control (optimal medical management) with active treatment (optimal medical treatment plus ASV)
 - Sample size: 1325 patients and 651 events
 - 91 active centres



> Patient Selection

- Severe heart failure
 - Symptoms on maximal therapy
- Moderate and Severe Central Sleep Apnea
 - AHI>15
- Systolic heart failure = HFrEF
 - Around 50% of HF, men, coronary disease
- Diastolic Heart Failure = HFpEF
 - Around 50% of HF, women, elderly, hypertensive, obese
 - Not studied in SERVE-HF

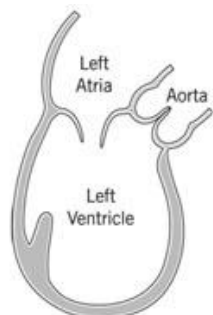


Figure 2
Systolic Heart Failure

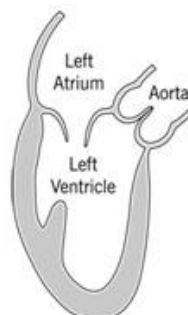


Figure 3
Normal Heart

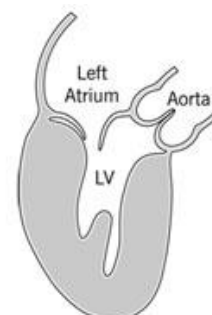


Figure 4
Diastolic Heart Failure

➤ Field Safety Notice — issued 13 May 2015

Numbers of events reached late April and analysis began

- Preliminary primary end-point analysis showed no significant difference between patients treated with ASV and those in the control group:
 - Time to all-cause mortality or unplanned hospitalization for worsening heart failure (HR =1.136 [0.974 - 1.325], p=0.104)
- However, there was a 2.5% absolute increased annual risk of cardiovascular mortality for those randomized to ASV therapy compared to the control group:
 - 10% of the ASV group experienced a CV death each year compared to 7.5% of the control group, (HR=1.335 [1.070-1.666), p=0.010).



➤ Field Safety Notice — issued 13 May 2015

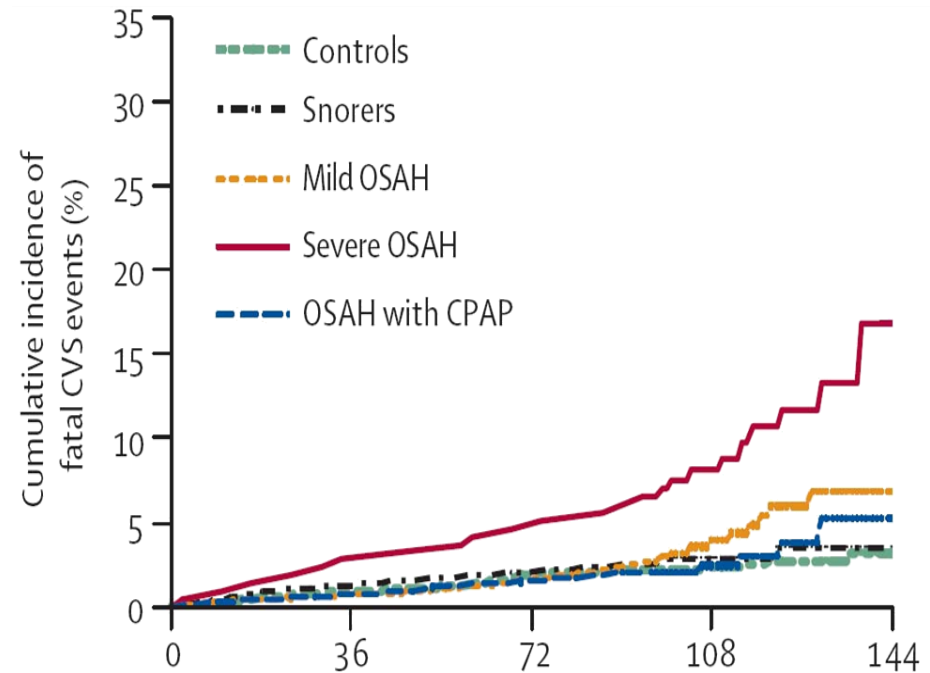
- The increased risk appears to be greater in those with more severe ventricular dysfunction
- The majority of excess mortality is due to death occurring out of hospital (likely sudden cardiac death).
- The risk does not diminish with time on therapy and is independent of perceived symptomatic benefit from therapy.
- Working with professional societies to reach patients at risk and with a tier one medical journal to expedite publication.



➤ PAP Therapy is Safe outside SERVE-HF patient group

- SERVE-HF population very different to other PAP users
- Untreated OSA is associated with increased CV mortality
- No safety signals among several large trials and several demonstrate a lowering of mortality with PAP therapy
- NIV reduces mortality in COPD
- Less information about ASV but no safety issues

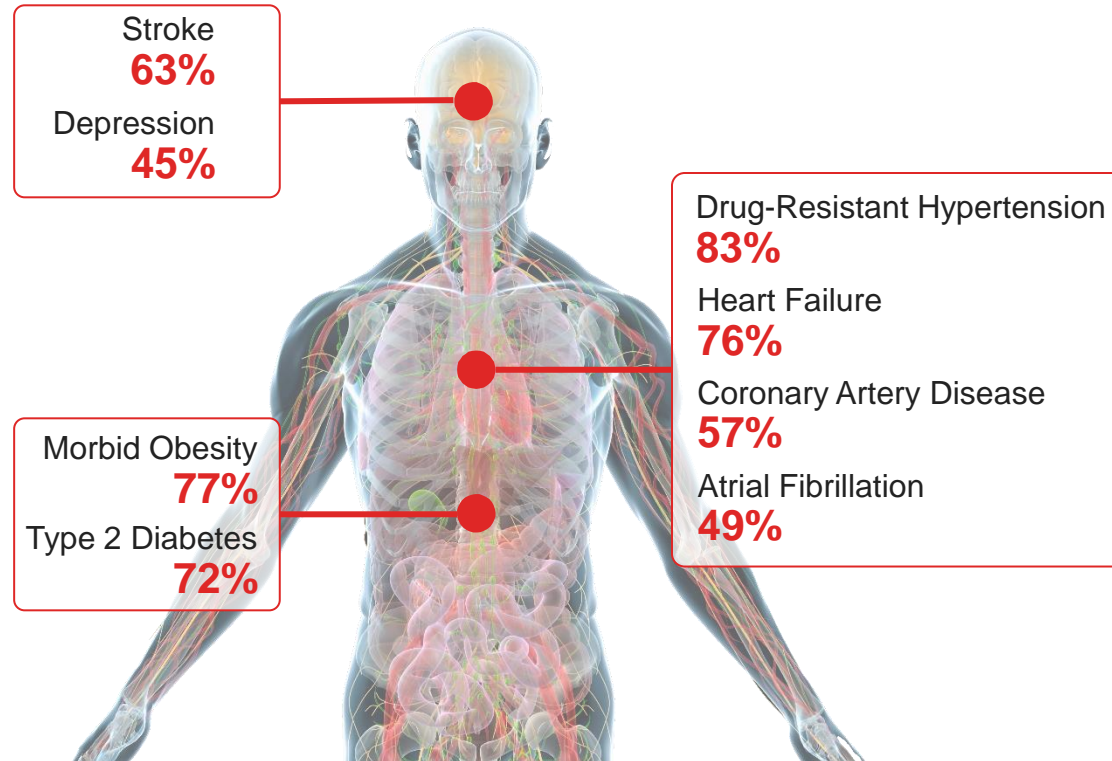
Marin et al, Lancet 2005;365:1046-53



SERVE-HF results only apply to its specific patient group



Sleep Apnea: Many clinical targets for ResMed to focus on



References: Logan et al. *J. Hypertension*; O'Keefe and Patterson, *Obes Surgery*; Oldenburg et al., *Eur J Heart Failure*; Einhorn et al. *Endocrine Prac*; Bassetti et al. *Stroke*

➤ Where are we going next in clinical research?

- Many opportunities exist to increase market size through demonstrating the influence of therapy on chronic diseases.
- ResMed remains committed to advancing the field through scientific research.





Thank you